Europäisches Patentamt | European Patent Office | Office européen des brevets

07. 10. 2004

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le 29 NOV 2004

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

EUROPÄISCHES PATENTAMT · EUROPEAN PATENT OFFICE · OFFICE EUROPÉEN DES BREVETS · DEN HAAG · 's-GRAVENHAGE

C. v.d. Aa-Jansen

Patentanmeldung Nr.
Patent application no.
Demande de brevet n° PCT/EP 03/11316

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: PCT/EP 03/11316

Anmelder:
Applicant(s):
Demandeur(s): 1. ACTELION PHARMACEUTICALS LTD - Allschwil, Switzerland

Bezeichnung der Erfindung:
Title of the invention: Novel diazabicyclononene derivatives and use thereof
Titre de l'invention:

Anmeldetag:
Date of filing: 13 October 2003 (13.10.2003)
Date de dépôt:

In Anspruch genommene Priorität(en)
Priority(ies) claimed
Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Benennung von Vertragsstaaten : Siehe Formblatt PCT/RO/101 (beigefügt)
Designation of contracting states : See Form PCT/RO/101 (enclosed)
Désignation d'états contractants : Voir Formulaire PCT/RO/101 (ci-joint)

Bemerkungen:
Remarks:
Remarques:

PCT REQUEST

Actel 54/R15

Original (for SUBMISSION) - printed on 09.10.2003 10:08:24 PM

III-3	**Applicant and/or inventor**	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	FISCHLI, Walter
III-3-5	Address:	Obertorweg 64 CH-4123 Allschwil Switzerland
III-4	**Applicant and/or inventor**	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	REMEN, Lubos
III-4-5	Address:	Kurzelängeweg 28 CH-4123 Allschwil Switzerland
III-5	**Applicant and/or inventor**	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	RICHARD-BILDSTEIN, Sylvia
III-5-5	Address:	12, rue des Beaux Prés F-68440 Dietwiller France
III-6	**Applicant and/or inventor**	
III-6-1	This person is:	inventor only
III-6-4	Name (LAST, First)	WELLER, Thomas
III-6-5	Address:	Hoelzlistrasse 58 CH-4102 Binningen Switzerland
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HOFMANN, Dieter
IV-1-2	Address:	StratAll Therwilerstrasse 87 CH-4153 Reinach Switzerland
IV-1-3	Telephone No.	+41 61 713 1560
IV-1-4	Facsimile No.	+41 61 713 1561
IV-1-5	e-mail	hofmanndrd@bluewin.ch
IV-1-5	Agent's registration No.	25510
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT

ACTELION 54/R15

Novel Diazabicyclononene Derivatives and Use thereof

The invention relates to novel compounds of the general formula **I**. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula **I** and especially their use as renin inhibitors in cardiovascular events and renal insufficiency. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might therefore be useful as inhibitors of plasmepsins to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159;

Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT_1 receptors. This may raise serious questions regarding the safety and efficacy profile of AT_1 receptor antagonists. In summary, renin inhibitors are not only expected to be different from ACE inhibitors and AT_1 blockers with regard to safety, but more importantly also with regard to their efficacy to block the RAS.

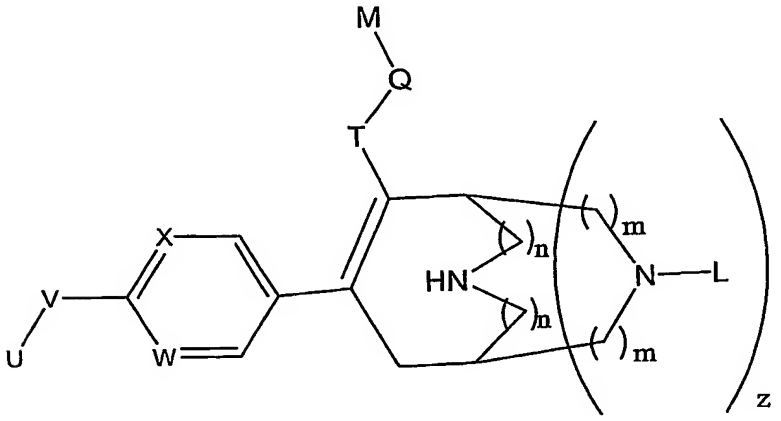
Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are missing and sought. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il*

Farmaco, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis are described.

The present invention describes non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula **I**,



Formula I

wherein

X and W represent independently a nitrogen atom or a -CH- group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5-$; heteroaryl-$O(CH_2)_vR^5-$; aryl-$O(CH_2)_2O(CH_2)_wR^5-$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5-$;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with

hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, CO-morpholin-4-yl, CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH^2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH^2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0, and in case n represents the integer 1, m is the integer 0;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;
v is the integer 2, 3, or 4;
w is the integer 1 or 2;
z is the integer 0 or 1

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula **I** – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl nad isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that

can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably methylenoxy, ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O_2)R1'$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$ whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR_1S(O_2)R^1$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$,

$-SO_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy, whereby $R^{1'}$ has the meaning given above. Preferred substituents are halogen, lower alkoxy, lower alkyl, CF_3, OCF_3.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $-COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower

alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $R^{1'}$ has the meaning given above.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

The term **sp3-hybridized** refers to a carbom atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula I can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts therof.
The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

A group of preferred compounds are compounds of general formula I wherein X, W, V, U, T, Q, L, M, v, and w are as defined in general formula I above and wherein

n is 0 and
m is 1.

Another group of preferred compounds of general formula **I** are those wherein X, W, V, U, T, Q, M, m, n, v, and w are as defined in general formula **I** above and

L represents H; $-COR^{3''}$; $-COOR^{3''}$; $-CONR^{2''}R^{3''}$;

whereby $R^{2''}$ and $R^{3''}$ represent independently lower alkyl, lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl - lower alkyl groups are unsubstituted or monosubstituted with halogen, cyano, hydroxy, $-OCOCH_3$, $-CONH_2$, -COOH, $-NH_2$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized.

Another group of preferred compounds of general formula **I** above are those wherein X, W, V, U, L, m, n, v, and w are as defined in general formula **I** and

T is $-CONR^1-$;
Q is methylene;
M is aryl-$O(CH_2)_vR^5-$; heteroaryl-$O(CH_2)_vR^5-$; aryl-$O(CH_2)_2O(CH_2)_wR^5-$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5-$.

Another group of even more preferred compounds of general formula **I** are those wherein X, W, U, L, T, Q, M, m, n, v, and w are as defined in general formula **I** above and

V is $-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$.

Another group of also more preferred compounds of general formula **I** are those wherein V, U, T, Q, M, L, m, n, v, and w are as defined in general formula **I** above and

X and W represent -CH-.

Another group of also more preferred compounds of general formula **I** are those wherein X, W, V, Q, T, M, L, m, n, v, and w are as defined in general formula **I** above and

U is a mono-, di-, or trisubstituted phenyl wherein the substituents are halogen; lower alkyl or lower alkoxy.

Especially preferred compounds of general formula **I** are those selected from the group consisting of:

(rac.)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide.

The compounds of general formula **I** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used in the treatment and/or prophylaxis of cardiovascular and

renal diseases. Examples of such diseases are hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. They can also be used to prevent restenosis after balloon or stent angioplasty, to treat erectile dysfunction, glomerulonephritis, renal colic, and glaucoma. Furthermore, they can be used in the therapy and the prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, as well as other diseases presently known to be related to the RAS.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure, which method comprises administrating a compound as defined above to a human being or animal.

The invention further relates to the use of compounds of general formula **I** as defined above for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure.

The compounds of formula **I** may also be used in combination with one or more other therapeutically useful substances e. g. with other renin inhibitors, with ACE-inhibitors, with angiotensin-receptor antagonists, with diuretics, with calcium channel blockers, with endothelin receptors antagonists or with other drugs

beneficial for the prevention or the treatment of cardiovascular events or renal insufficiency.

All forms of prodrugs leading to an active component comprised by general formula **I** above are included in the present invention.

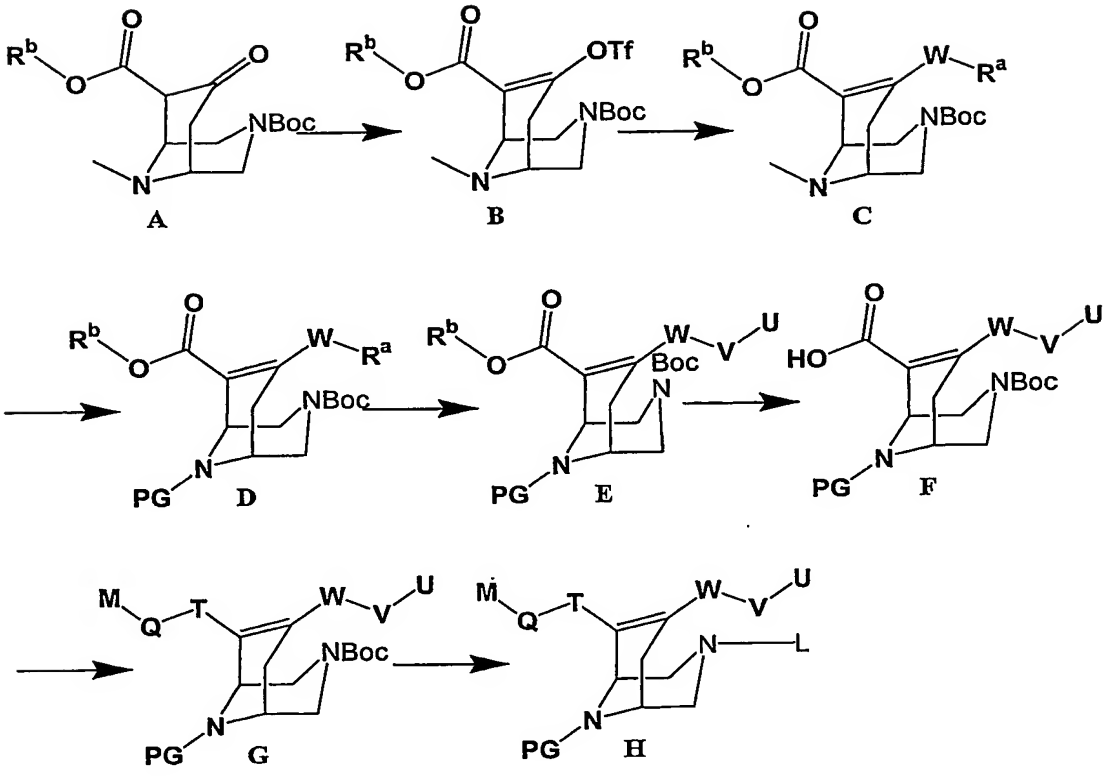
The compounds of general formula **I** can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Preparation of the precursors:

Precursors are compounds which were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry. Most of the chemistry applyable here has already been described in other patent applications.

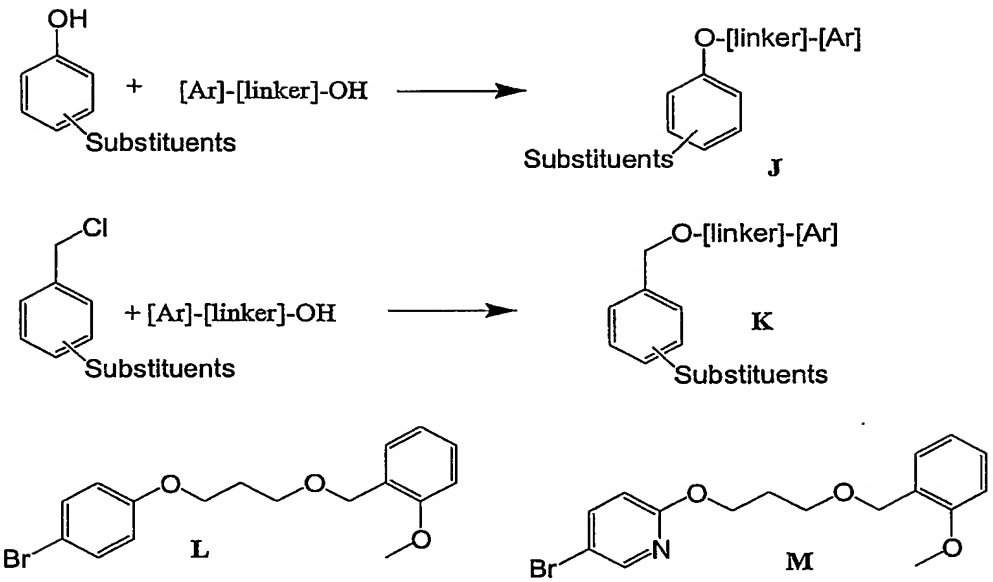
As illustrated in Scheme 1 the known compound **A** can be derivatised into the corresponding triflate **B**. A *Negishi*-type coupling (or any other coupling catalysed by a transition metal) would lead to a compound of type **C**. After protecting group manipulation (→ compound of type **D**), ajustement of the W-V-U linker would be possible for instance by deprotection and a *Mitsunobu*-type reaction, leading to a compound of type **E**. Hydrolysis of the ester would lead to a carboxylic acid of type **F**, then amide coupling for instance to a compound of type **G**. Removal of the Boc-protecting group and alkylation, or acylation, would lead to a precursor of type **H**.

Scheme 1



The bromoaryl components can be prepared as described in Scheme 2. A *Mitsunobu* coupling (→ compounds of type **J**) or the alkylation of an alcohol with a benzylic chloride (or bromide, → compounds of type **K**) are often the most convenient methods. Derivatives **L** and **M** were prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397) or 3-(5-bromopyridin-2-yloxy)propan-1-ol (Patent Application WO 98/39328) according to these methods. Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, might be used as well (see e.g. March, J, "Advanced Organic Chemistry,", 3rd ed., John Wiley and sons, 1985).

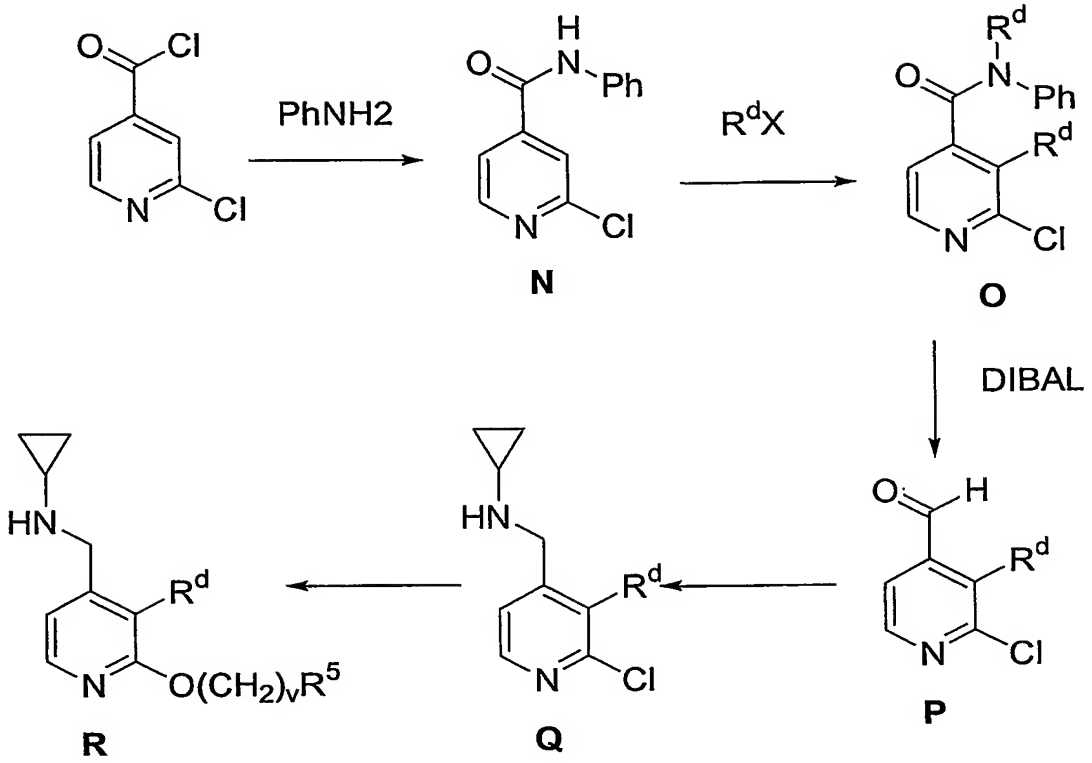
Scheme 2



Preparation of the secondary amines

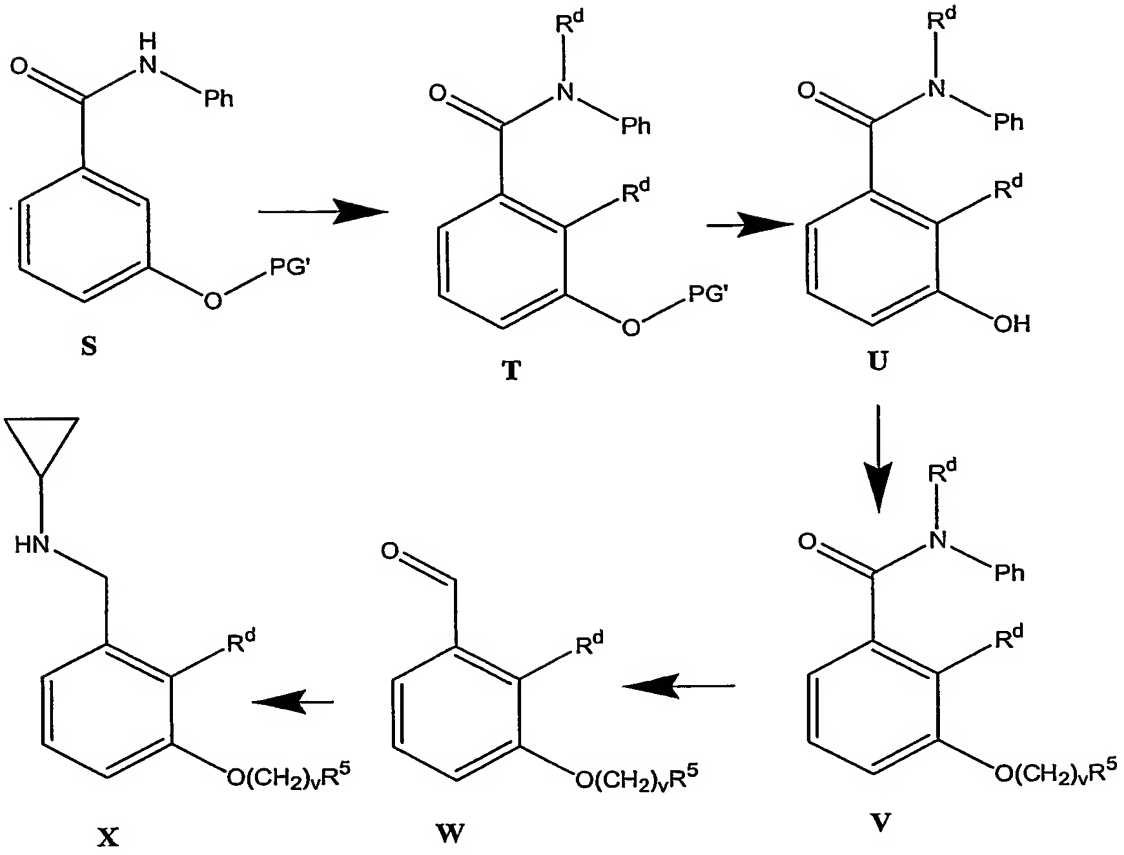
The secondary amines can be prepared for instance as described in Scheme 3. The pyridine derivative **N** can be prepared from commercially avialable 2-chloro-isonicotinoyl chloride. Deprotonation at the 3-position of this derivative, for instance with BuLi, and subsequent alkylation with a suitable electrophile could lead to a derivative of type **O**, whereas R^d represents a suitable that can be introduce by this chemistry, and may be transformed later into a desired substituent a described in general formula I. Reduction of the amide into al aldehyde with DIBAL could lead to a compound of type **P**, then a reductive amination would lead to an amine of type **Q**. Finally substitution of the chlorine atom with an alcohol of type $HO(CH2)_vR^5$, where as R^5 may still be protected, would lead to an amine of type **R**. Of course an alcohol of type $HO(CH_2)_2O(CH_2)_wR^5$ could be introduced in the way.

Scheme 3



In the case of phenyl derivatives it would be better to start from a compound of type **S**, whereas PG' represents a suitable protecting group. Alkylation would lead to a drivative of type **T**, then deprotection to a derivative of type **U**. Ether bond formation, via a Mitsunobu-type reaction or from a correponding alkyl halide, would lead to a compound of type **V**. Reduction would lead to an aldehyde of type **W**, then reductive amination to an amine of type **X**.

Scheme 4

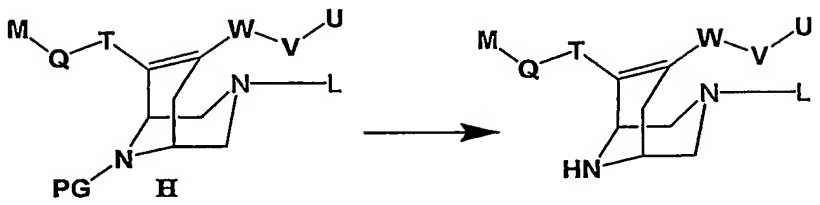


Preparation of final compounds

From precursors prepared as described above, the final compounds can be prepared using parallel chemistry techniques. For the specific examples, see the experimental part.

Diazabicyclononenes of type of **H** can be deprotected using standard procedures (Scheme 5). Purification by preparative HPLC might give the corresponding TFA salts or formate salts.

Scheme 5



The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid poyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for

example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula **I** can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula **I**.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

General remarks

The compounds were characterized at least by LC-MS and ^{1}H-NMR. Only the LC-MS data are given here.

Abbreviations

ACE	Angiotensin Converting Enzyme
AcOH	Acetic acid
Ang	Angiotensin
aq.	aqueous
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
conc.	concentrated
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
MeOH	Methanol
org.	organic
PG	protecting group
RAS	Renin Angiotensin System
RP18	Reversed phase column, filled with C_{18} hydrocarbon
rt	room temperature
sol.	Solution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
tBuOH	*tert*-Butanol
tBuOK	Potassium *tert*-butylate

Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Preparation of the precursors

(*rac.*)-(*1R, *5S**)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B)**

A sol. of bicyclononanone **A** (2.22 g, 6.80 mmol) in THF (50 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 326 mg, about 8.2 mmol) was added. A gas evolution was observed. After 20 min, Tf_2NPh (3.22 g, 9.00 mmol) was added. 10 min later, the ice bath was removed. After 3 h, the sol. was diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 3:1 → EtOAc) yielded the title compound as an oil (2.50 g, 80%). $R_f = 0.15$ (EtOAc/heptane 1:1). LC-MS: $R_t = 4.73$; ES+: 458.95.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (C1)**

A solution of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 46.11 g, 0.140 mol) in dry THF (750ml) was cooled to –78°C. BuLi (1.6M in hexane, 96mL, 143 mmol) was added, and the reaction mixture was stirred for 1 h at –78°C. $ZnCl_2$ (1M in THF, 210mL, 210 mmol) was added, and the solution was allowed to warm up at r.t. Vinyl triflate **B** (31.1 g, 70.0 mmol) and $Pd(PPh_3)_4$ (2.03 g, 1.75 mmol) were added and the mixture was heated to reflux. After 6 h the mixture was allowed to cool to rt. The mixture was diluted with EtOAc (2000 mL) and washed with aq.

1M NaOH (~1000mL). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH_2Cl_2 / MeOH; 49:1 → 45:5) yielded the title compound (33.02 g, 84%).

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (C2)**

A solution of [2-(4-bromo-phenoxy)ethoxy]-*tert*-butyldimethylsilane (Morita, C.; et al.al.; *Heterocycles*, **2000**, *52*, 1163; 47.7 g, 0.144 mol) in dry THF (650mL) was cooled to –78°C. BuLi (1.6M in hexane, 92.2 mL, 147 mmol) was added, and the reaction mixture was stirred for 1 h at –78°C. $ZnCl_2$ (0.83 M in THF, 260 mL, 216 mmol) was added, and the solution was allowed to warm up at r.t. Vinyl triflate **B** (33.0 g, 72.0 mmol) in THF (100 mL) and $Pd(PPh_3)_4$ (2.08 g, 1.80 mmol) were added and the mixture was heated to reflux. After 30 min the mixture was allowed to cool to rt. The mixture was diluted with EtOAc and washed with aq. 1M NaOH. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH_2Cl_2 / MeOH; 49:1 → 45:5) yielded the title compound (33.9 g, 84%).

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (D1)**

1–Chloroethyl chloroformate (50.8 mL, 470 mmol) and $NaHCO_3$ (39.5 g, 470 mmol) were added to a sol. of bicyclooctene **C1** (26.3 g, 57.0 mmol) in 1,2-dichloroethane (450 mL). The sol. was heated to reflux. After 3 h, the reaction mixture was allowed to cool to rt, filtered, and the solvents were removed under reduced pressure. MeOH (210 mL) was added. The mixture was stirred at 60 °C for 60 min, and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (460 mL), DIPEA (40.3 mL, 235 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (30.8 g, 141 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt overnight. The mixture was washed

with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (13.6 g, 54%).

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (D2)**

1-Chloroethyl chloroformate (51.7 mL, 474 mmol) and $NaHCO_3$ (40.0 g, 474 mmol) were added to a sol. of bicyclooctene **C2** (26.6 g, 47.4 mmol) in 1,2-dichloroethane (500 mL). The sol. was heated to reflux. After 3 h, the reaction mixture was allowed to cool to rt, filtered, and the solvents were removed under reduced pressure. MeOH (500 mL) was added. The mixture was stirred at 50 °C for 20 min, and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (500 mL), DIPEA (40.6 mL, 237 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (31.4 g, 142 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (16.6 g, 66%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (E1)**

To a sol. of compound **D1** (16.45 g, 30.9 mmol) in dry toluene (350 mL) was added 2-chloro-3,6-difluorophenol (10.2 g, 62 mmol), azodicarboxylic dipepiridide (15.65 g, 62 mmol) and tributylphosphine (85%, 24.15 mL, 93 mmol). The mixture was heated to reflux for 1 h and allowed to cool to rt. The mixture was diluted with EtOAc, and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc / heptane 5% → 1:1) yielded the title compound (20.2 g, 96%) as a yellow oil.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (E2)**

To a sol. of compound **D2** (16.6 g, 30.2 mmol) in dry toluene (500 mL) was added 2,6-dichloro-*p*-cresol (11.1 g, 62.5 mmol), azodicarboxylic dipepiridide (15.8 g, 62.5 mmol) and tributylphosphine (85%, 27.2 mL, 93.7 mmol). The mixture was heated to reflux for 4 h and allowed to cool to rt. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc / heptane 5% → 1:1) yielded the title compound (12.3 g, 57%) as a yellow oil.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (F1)**

A sol. of compound **E1** (12.3 g, 17.8 mmol) in EtOH (860 mL) and aq.1M NaOH (370 mL) was stirred at 80°C overnight. The reaction mixture was partially concentrated under reduced pressure and the residue was acidified with aq. 3M HCl. The mixture was extracted with EtOAc (3x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was used without further purification.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (F2)**

A sol. of compound **E2** (20.17 g, 29.8 mmol) in EtOH (1000 mL) and aq.1M NaOH (550 mL) was stirred at 80°C for 5 h. The reaction mixture was partially concentrated under reduced pressure and the residue was acidified with aq. 1M

HCl. The mixture was extracted with EtOAc (3x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was used without further purification.

(*rac.*)-(*1R, *5S**)-6-({2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G1)**

A sol. of compound **F1** (45.5 mg, 0.070 mmol), amine **R1** (71 mg, 0.21 mmol), HOBt (12 mg, 0.088 mmol), EDC.HCl (34 mg, 0.175 mmol) DIPEA (0.048 ml, 0.28 mmol)and DMAP (2.1 mg, 0.18 mmol) in CH_2CL_2 (2 mL) was stirred at rt for 24 h. EDC.HCl (27 mg, 0.14 mmol) and DIPEA (0.012 mL, 0.07 mmol) were added again, and the mixture was stirred at rt for 7 h. One more time EDC.HCl (27 mg, 0.14 mmol) and DIPEA (0.012 mL, 0.07 mmol) were added and the mixture was stirred at rt for additional 4 days. The mixture was loaded over an isolute column (pre-conditionned with aq. 1M HCl, 1 mL). The column was washed with CH_2Cl_2 (4 mL), and the org. extracts were dried over $MgSO_4$, filterd, and the solvents were removed under reduced pressure. The crude (106 mg) was used in the next reaction without purification. LC-MS:R_T = 1.35 min; ES^+ = 967.5.

(*rac.*)-(*1R, *5S**)-6-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4ylmethyl}cyclopropylcarbamoyl)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G2)**

As described for compound **G1**, but from compound **F1** (45.5 mg, 0.070 mmol), amine **R2** (74 mg, 0.21 mmol), DIPEA (0.048 mL, 0.28 mmol), DMAP (2.1 mg, 0.018 mmol), HOBt (12 mg, 0.088 mmol), EDC·HCl (34 mg, 0.175 mmol) and CH_2Cl_2 (2 mL). The crude (94 mg) was used in the next reaction without purification. LC-MS:R_T = 1.36 min.

(*rac.*)-(*1R, *5S**)-6-({2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-7-{4-[2-(2,6-dichloro-4-methyl-phenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G3)**

As described for compound **G1**, but from compound **F2** (46.5 mg, 0.070 mmol), amine **R1** (71 mg, 0.21 mmol), DIPEA (0.048 mL, 0.28 mmol), DMAP (2.1 mg, 0.018 mmol), HOBt (12 mg, 0.088 mmol), EDC·HCl (34 mg, 0.175 mmol) and CH_2Cl_2 (2 mL). The crude (94 mg) was used in the next reaction without purification. LC-MS:R_T = 1.35 min.

(*rac.*)-(*1R, *5S**)-6-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-7-{4-[2-(2,6-dichloro-4-methyl-phenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G4)**

As described for compound **G1**, but from compound **F2** (46.5 mg, 0.070 mmol), amine **R2** (74 mg, 0.21 mmol), DIPEA (0.048 mL, 0.28 mmol), DMAP (2.1 mg, 0.018 mmol), HOBt (12 mg, 0.088 mmol), EDC·HCl (34 mg, 0.175 mmol) and CH_2Cl_2 (2 mL). The crude (94 mg) was used in the next reaction without purification. LC-MS:R_T = 1.36 min.

2-Chloro-*N*-phenylisonicotinamide (N)

To the sol. of 2-chloro-isonicotinoyl chloride (10 g, 56.8 mmol) in 1,2-dichloroethane (100 mL) was added at 0 °C a sol. of aniline (5.70 mL, 62.5 mmol) and DIPEA (10.2 ml, 59.6 mmol) in 1,2-dichloroethane (10 ml) during ca. 30 min. The reaction was stirred at 0 °C for ca. 30 min and subsequently for 1 h at 95 °C. Water (30 mL) was added at rt and the product was filtered-off. The water phase was extracted with CH_2Cl_2 (200 mL) and the solvents were removed under reduced pressure. The residue was crystallized from MeOH/water 1:10 (110

mL), yielding the titlc compound (12.12 g, 92%).LC-MS: R_T = 0.87 min; ES^+ = 233.1.

2-Chloro-3-*N*-dimethyl-*N*-phenyl-isonicotinamide (O)

To the sol. of compound **N** (8.79g, 37.8 mmol) in THF (90 mL) was added BuLi (1.6M in hexane, 52 mL, 83.2 mmol) at –78°C. After 30 min MeI (7.70 mL, 124 mmol) was added dropwise at the same temperature. After 1 h water (100 mL) was added and the mixture was extracted with Et_2O (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. Purification by FC yielded the title compound (8.67 g, 88%). LC-MS:R_T = 0.85 min; ES^+ = 261.2.

2-Chloro-3-methylpyridine-4-carbaldehyde (P)

To the sol. of pyridine derivative **O** (9.58 g, 36.7 mmol) in CH_2Cl_2 (190 mL) was at –78 °C added DIBAL (1M in CH_2Cl_2, 55.1 mL, 55.1 mmol), and the mixture was stirred at –78 °C for 1.5 h. Aq. sat. tartaric acid monosodium monokalium salt in water (20 ml) was added and the mixture was allowed to warm up to rt. Water was added and the mixture was extracted with CH_2Cl_2. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.4 g, 77%). LC-MS:R_T = 0.76 min; ES^+ = 156.1.

(2-Chloro-3-methylpyridin-4-ylmethyl)-cyclopropylamine (Q)

A sol. of aldehyde **P** (4.70 g, 30.2 mmol) and cyclopropylamine (4.20 ml, 60.4 mmol) in MeOH (65 mL) was stirred at rt for 4 h. $NaBH_4$ (1.55 g, 39.2 mmol) was added and the mixture was stirred at rt for 12 h. Water and subsequently aq. 1M NaOH were added, and the solvents were partially removed under reduced pressure. The water phase was extracted with CH_2Cl_2 (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under

reduced pressure. Purification of the crude by FC yielded the title compound (4.66 g, 79%). LC-MS:R_T = 0.43 min; ES^+ = 197.1.

{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]-3-methylpyridin-4-ylmethyl}-cyclopropylamine (R1)

A sol. of amine **Q** (1.30 g, 6.61 mmol) and 2-(*tert*-butyldimethylsilanyloxy)-ethanol (423 mg, 10.58 mmol) in dioxan (5 ml) was heated at 115 °C for 12 h. The solvents were removed under reduced pressure, water was added, and the mixture was extracted with Et_2O (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title compound (926 mg, 42%). LC-MS:R_T = 0.79 min; ES^+ = 337.3.

{2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methylpyridin-4-ylmethyl}-cyclopropylamine (R2)

A sol. of amine **Q** (1.24 g, 6.30 mmol) and 2-(*tert*-butyldimethylsilanyloxy)-propan-1-ol (403 mg, 10.1 mmol) in dioxan (5 ml) was heated at 115 °C for 12 h. The solvents were removed under reduced pressure, water was added, and the mixture was extracted with Et_2O (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title compound (192 mg, 9%). LC-MS:R_T = 0.84 min; ES^+ = 351.4.

Preparation of the final compounds

Example 1

***(rac.)*-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide**

To a sol. compound **G2** (106 mg, ca. 0.07 mmol) in CH_2Cl_2 (1 ml) was added 4M HCl in dioxan (1 mL) at 0 °C, and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure and the crude was dried under high vacuum. Purification of the crude by HPLC yielded the title compound as dihydrochloride (12.6 mg, 24 %). LC-MS: $R_T = 0.78$ min; $ES^+ = 667.43$.

Example 2

***(rac.)*-(*1R**, *5S**)-7-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide**

To a sol. compound **G4** (166 mg, ca. 0.07 mmol) in CH_2Cl_2 (1 ml) was added 4M HCl in dioxan (1 mL) at 0 °C, and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure and the crude was dried under high vacuum. Purification of the crude by HPLC yielded the title compound as dihydrochloride (12.6 mg, 24 %). LC-MS: $R_T = 0.78$ min; $ES^+ = 681.41$.

Example 3

***(rac.)*-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide**

To a sol. compound **G1** (106 mg, ca. 0.07 mmol) in CH_2Cl_2 (1 ml) was added 4M HCl in dioxan (1 mL) at 0 °C, and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure and the crude was dried under high vacuum. Purification of the crude by HPLC yielded the title compound as dihydrochloride (12.6 mg, 24 %). LC-MS: $R_T = 0.77$ min; $ES^+ = 653.39$.

Example 4

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide**

To a sol. compound **G3** (166 mg, ca. 0.07 mmol) in CH_2Cl_2 (1 ml) was added 4M HCl in dioxan (1 mL) at 0 °C, and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure and the crude was dried under high vacuum. Purification of the crude by HPLC yielded the title compound as dihydrochloride (12.6 mg, 24 %). LC-MS: $R_T = 0.77$ min; $ES^+ = 667.41$.

The following assay was carried out in order to determine the activity of the compounds of general formula **I** and their salts.

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 µL per well of an enzyme mix and 2.5 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

• human recombinant renin (0.16 ng/mL) • synthetic human angiotensin(1-14) (0.5 µM)

• hydroxyquinoline sulfate (1 mM)

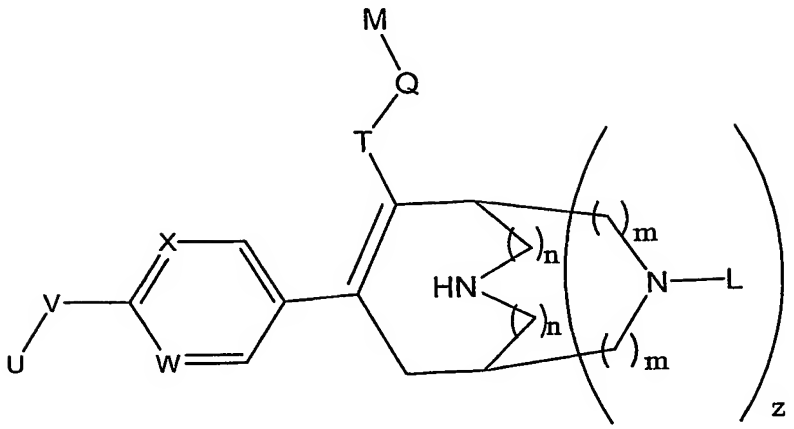
The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 µL of Ang I-antibodies in essaybuffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were

washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 100 nM. However selected compounds exhibit a very good bioavailibility and are metabolically more stable than prior art compounds.

Claims

1. Compounds of the general formula I



Formula I

wherein

X and W represent independently a nitrogen atom or a -CH- group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$-; heteroaryl-$O(CH_2)_vR^5$-; aryl-$O(CH_2)_2O(CH_2)_wR^5$-; heteroaryl-$(CH_2)_2O(CH_2)_wR^5$-;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, $-OCOR^2$, $-COOR^2$, lower alkoxy, cyano, $-CONR^2R^{2'}$, $-NH(NH)NH^2$, $-NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represents hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; $-COOR^2$; $-CONH_2$;

R^5 represents –OH, $-OCOR^2$, $-COOR^2$, $-NR^2R^{2'}$, $-OCONR^2R^{2'}$, $-NCONR^2R^{2'}$, cyano, $-CONR^2R^{2'}$, SO_3H, $-SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), $-NH(NH)NH^2$, $-NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0, and in case n represents the integer 1, m is the integer 0;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;
v is the integer 2, 3, or 4;
w is the integer 1 or 2;
z is the integer 0 or 1;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds of general formula **I** wherein X, W, V, U, T, Q, L, M, v, and w are as defined in general formula **I** and

n is 0
m is 1,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds of general formula **I** wherein X, W, V, U, T, Q, M, m, n, v, and w are as defined in general formula **I** and

L represents $-COR^{3''}$; $-COOR^{3''}$; $-CONR^{2''}R^{3''}$;

$R^{2''}$ and $R^{3''}$ represent independently lower alkyl; lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl-lower alkyl are undubstituted or mono-substituted with halogen, -CN, -OH, $-OCOCH_3$, $-CONH_2$,-COOH, or $-NH_2$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

4. Compounds of general formula **I** wherein X, W, V, U, L, m, n, v, and w are as defined in general formula **I** and

T represents $-CONR^1-$;
Q represents methylene;
M represents aryl-$O(CH_2)_vR^5-$; heteroaryl-$O(CH_2)_vR^5-$; aryl-$O(CH_2)_2O(CH_2)_wR^5-$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5-$;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

5. Compounds of general formula **I** wherein X, W, U, L, T, Q, M, m, n, v, and w are as defined in general formula **I** and

V represents $-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

6. Compounds of general formula I wherein V, U, T, Q, M, L, m, n, v, and w are as defined in general formula I and

X and W represent a -CH- group

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

7. Compounds of general formula I wherein X, W, V, Q, T, M, L, m, n, v, and w are as defined in general formula I and

U is a mono-, di-, or trisubstituted phenyl whereby the substituents are halogen; lower alkyl or lower alkoxy

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

8. The compounds according to any one of claims 1 - 7 selected from the group consisting of

(rac.)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide;

(rac.)-(*1R**, *5S**)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(2-hydroxy-ethoxy)-3-methylpyridin-4-ylmethyl]amide.

9. Pharmaceutical compositions containing a compound of any one of claims 1 - 8 and usual carrier materials and adjuvants for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin-angiotensin system (RAS), comprising cardiovascular and renal diseases hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

10. A method for the treatment or prophylaxis of diseases which are related to the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases which are related to the RAS, which method

comprises administrating a compound according to any one of claims 1 to 8 to a human being or animal.

11. The use of compounds according to any one of claims 1 to 8 for the treatment or prophylaxis of diseases which are associated with the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

12. The use of one or more compounds of any one of claims 1 to 8 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, for the treatment of disorders as set forth in any one of claims 9 to 11.

ABSTRACT

The invention relates to novel 3,9-diazabicyclo[3.3.1]nonene derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.